P-22 Identification of Novel Serotonin Transporter Compounds by Virtual Screening and Experimental Verification

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The serotonin transporter (SERT) is located in the membranes of presynaptic neurons and plays an important role in the regulation of serotonergic neurotransmission by removing serotonin from the synaptic cleft. SERT is also the main target of the tricyclic and selective serotonin reuptake inhibitor (TCA and SSRI, respectively) groups of antidepressant drugs.

Here we present a SERT virtual screening (VS) protocol that was used to screen the Enamine, ChemBridge, ChemDiv, Asinex and Life Chemicals databases in order to detect novel SERT inhibitors. The protocol combines ligand-based (incl. 3D pharmacophore models) and structure-based screening approaches (flexible docking into multiple conformations of the ligand binding site detected in an outward-open SERT homology model), and biological evaluation of the virtual hits.

Using this multi-step combined VS protocol, 400 compounds were biologically evaluated, of which 100 in full binding studies. Our results show that 45 compounds had a K_i < 1000 nM.